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My main scientific interest is to understand the neurobiology and function of single genes and neurotransmitter systems involved in the regulation of motivation and mood, how they react to environmental influences, and their role in pathophysiological mechanisms that contribute to mental illnesses such as anxiety, depression and substance use disorders (SUDs). It is my strong believe that only by a better understanding of the aberrant long-term neuroplasticity underlying psychiatric disorders we will be able to overcome the present stagnation in medication development in the field. In the past years I have focused on long-term changes in brain neuroplasticity underlying alcohol use disorder (AUD) and on the discovery of novel pharmacological treatment targets as e.g. corticotropin-releasing hormone receptor subtype 1 (CRHR1), oxytocin, mu-opioid receptor, metabotropic glutamate receptor 2 (mGluR2) and L-type calcium channel subtype Cav1.2. Over the years, I developed skills in a broad spectrum of methods and a well-built track record in the fields of molecular neuroscience, functional neuroanatomy, and behavioral pharmacology. One highlight in my scientific carrier was that my research directly contributed to the initiation of clinical trials for CRHR1 antagonists for the treatment of AUD at the NIAAA.

I studied Biology at the University of Hamburg with focus on molecular biology and genetics. In my diploma thesis I became interested in transgenic animal models. Between the years from 1992 to 1997 (after and before giving birth of my two children) I worked as a scientific assistant on the brain renin-angiotensin system - a collaboration project between the Karolinska Institutet in Stockholm/Sweden (Prof. Kjell Fuxe) and the Max-Delbrück Center for Molecular Medicine in Berlin (Prof. Detlef Ganten). In 1997 I got awarded for a full-time PhD position at the Karolinska Institutet and started my PhD training under supervision of Prof. Fuxe at the Neuroscience Department, Karolinska Institutet. As a PhD student I first became interested in mechanistic aspects of stress specifically focusing on the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) regulation, their differential biological effects upon activation as well as their ability to modulate brain plasticity via regulating neurotrophic factors. During these years I got an excellent training in molecular neuroscience and neuroanatomy, and became later more interested to translate my interest in stress systems into animal models of addiction.

In my first years of postdoctoral training I was working on molecular mechanisms of maladaptive stress responses in animal models of alcoholism and got introduced to behavior neuroscience. I came to the NIAAA/NIH (USA) as a Research Fellow in 2004 and studied extra-hypothalamic corticotropin-releasing hormone (CRH) systems and other stress systems (e.g., nociceptin, neuropeptide Y as well as MR and GR) in alcohol dependent rodents. The findings on CRHR1 have contributed to the establishment of a role for the amygdala CRH

system in addiction, and have led to the initiation of two clinical trials for CRHR1 antagonists for the treatment of AUD. I worked further on neuroplasticity underlying experimentally induced chronic states of hyper-anxiety in rodents and had successfully set up robotic liquid handling system for quantitative high-throughput *in situ* hybridization and receptor autoradiography application as well as got introduced to high-throughput drug screening procedures.

After years as a postdoctoral researcher, both at the Karolinska Institutet (Sweden) and at the NIAAA/NIH (USA), I was offered to join Prof. Spanagel's team at the Institute of Psychopharmacology/CIMH. The CIMH is one of the best psychiatric research center worldwide and offer excellent conditions for top-level research. Obviously, the decision to leave the well-funded and renowned NIH lab and to start in a very different scientific environment was challenging. However, I was able to receive a research grant from the DFG for my own position, research staff and later became a group leader (RG Neuroanatomy). Since then my research focused on 1) identifying and functional validating novel candidate genes or biomarkers for psychiatric disorders, 2) providing proof-of-concept for the involvement of neuronal ensembles in SUDs, 3) studying the underlying mechanism of habitual/compulsive behavior in AUDs, and 4) working along the new concept on receptor heteromerization. Thus, all these strategies have the potential to identify new targets for medication development for SUDs.

I also developed several translational projects to test hypotheses from rodent models in human postmortem (PM) material and vice versa. In our translational approach we used advanced transgenic animal models combined with viral gene transfer for anatomical, cellular, behavioral, and global network activity pattern analysis. I have a large collection of human brain tissues from deceased patients suffering under SUD for alcohol, tobacco, cocaine, cannabis as well as from healthy control individuals and are currently enlarging and extending our tissue samples by collecting new PM samples from established brain banks and collaboration partners. PM brain tissues were used for e.g. multi-omics experiments for genome-wide genetic, epigenetic and transcriptome analysis. With this multi-disciplinary research approach, the mechanisms of SUD can be better understood and ultimately new targets for relapse-prevention therapies can be found.

Over the years I have established strong and fruitful relations with several international and national labs. **International collaborations**: G. Bakalkin (Uppsala University, Sweden), E. Carbone (University Torino, Italy), R. Ciccocioppo (University Camerino, Italy), R. Costa (Allen Institute, USA), K. Fuxe (Karolinska Institutet, Sweden), M. Heilig (Linköping University, Sweden), N.J. Justice (Baylor College of Medicine, Houston, USA), A. Mathé, (Karolinska Institutet, Sweden), O. Kärkkäinen (University Kuopio, Finland), P. Hyytiä (University Helsinki, Finland), M. Pérez de la Mora (Universidad Nacional Autónoma de Mexico, Mexico), R. Rimondini (University Bologna, Italy). **National collaborations:** M. Bader (Max-Delbrück-Center for Molecular Medicine, Berlin), J. Deussing (MPI, Munich), H.-C. Pape (Westfälische Wilhelms Universität, Münster), A. Schmitt and P. Falkai (Munich Center for Neuroscience). I further have active in-house collaborations with preclinical (V. Grinevich, D. Bartsch, W. Kelsch, M. Rietschel), and clinical (F. Kiefer, S. Vollstädt-Klein) scientists at the CIMH.

From 2017 to 2021 I have acted as a Chair, co-Chair and member of the Swedish Research Council (SRC) for the Mental Health and Psychiatry panel. I was member of the director board of the German Collaborative Center Network Research SFB1134 (from 2015 to 2018), and

since 2013 member of the NSW brain bank network (NSWBBN) Scientific Review Committee (SRC) and Tissue Review Panel (TRP), Sydney, Australia.

Most importantly, I was able to obtain research funding from DFG, SFB, BMBF, Hetzler foundation for a total of 2.9 Million Euros, which allowed me to continue my research and support of my staff.

To date I supervised 6 PhD students, 10 Master - and 8 Bachelor students as well as a variety of internship students. I like the scientific interaction with young researchers and students. That was mirrored also in my teaching activities over the last years. Since 2018 I have been organizing the “Reward and Addiction Seminar” at the IoP/CIMH for neuroscience master students from the University of Heidelberg and students from the Center for Biomedicine and Medical technology Mannheim. The yearly student’s evaluation were overwhelming positive with comments as e.g. ’very interesting and informative seminar‘ to more enthusiastic remarks as ’the choice of topics was very exciting. I learned a lot- and most importantly I was able to broaden my horizons in this field. Thank you very much for the organization!’. Thus, we mostly received highest marks for the seminar. During my years at the CIMH I was involved also in teaching activities such as Neuroanatomy lectures and seminars for medical students at UMM (MaReCum, Universitätsklinik Mannheim), and organized seminars e.g. „Current Topics in Addiction Research“ and „Psychopharmacology“ at IoP/CIMH.

Finally, I am currently authorized radioactivity officer in the lab building at the CIMH and was member of the vaccination team at the CIMH during the COVID-19 pandemic period.

Key output of the years 2020-now:

1. Multi-omics data from GWAS, EWAS and RNA Sequencing had been generated from bulk tissues of human PM brains from AUDs and control individuals. Using a comparative and integrative computational approach, these data led to 3 publications by Zillich et al. (all published in 2022).
2. In another translational study we examined mGluR2 in alcohol addiction. Here, a mGluR2 deficit was counteracted by psilocybin treatment for cue-induced relapse-like behavior (Meinhardt et al. 2021, Science advanced). Thus, psilocybin treatment may provide an effective strategy for relapse prevention in AUD, and a biomarker strategy for personalized treatment of individuals with mGluR2 deficit was recommended.
3. Further investigations have been undertaken regarding the oxytocin neuropeptide system. A previous study showed that oxytocin and its receptor are strongly altered in male individuals, and administration of oxytocin prevents cue-induced relapse-like behavior to alcohol drinking. In contrast, no changes in the oxytocin system were found in both female AUDs and female dependent rats (Hansson & Spanagel, 2020). Based on these observations we recommended oxytocin as an anti-relapse medicine for male AUDs.
4. Sex-differences had also been found in animals that had been experienced social rejection during early adolescence. As a result, adult female rats appeared to be more likely to alcohol drinking relapse-like behavior than male rats (Surakka et al., 2021). The underlying mechanisms have not yet been clarified, but are probably been associated with stress vulnerability factors.
5. Since alcohol intake increases craving to smoke tobacco, AUD and nicotine dependence show a high comorbidity (>80%). In a new animal model we could demonstrate, that chronic nicotine administration greatly increases alcohol consumption via the mu-opioid receptor

(Domi et al., 2020). This mechanism could presumable be important in the development of comorbid AUDs.

6. In another study we found, that alcohol dependence and circadian rhythmicity had a strong impact on b-Arrestin 2 (bArr2) expression, which in turn regulates the mu-opioid receptor as target for pharmacotherapeutic interventions in AUD. Our data described a new molecular mechanism, suggesting a critical role for bArr2 within the mesocorticolimbic system in alcohol dependence, which may further have implications for the development of novel bArr2-related treatment targets for AUD (Meinhardt et al., 2021).
7. We further analyzed habitual and goal-directed responses in alcohol-dependent rats and found that dependence produced a bias towards habitual responses to a natural reward (Giannone et al., 2022).
8. In another study we found evidence on heteromerization of dopamine D1 receptor with CRHR1 in vitro. Interaction of these two receptors seemed to regulate anxiety-like responses and dependence-induced stress vulnerability.
9. A candidate gene approach for SARS-CoV2 infection-relevant genes was carried out as part of a COVID-19 study. Here we showed differentially expressed genes in tissue samples of alcohol-dependent and non-dependent animals.

At last, but worth to mention - my work and expertise in the field has been reported in public media (https://www.quarks.de/gesellschaft/psychologie/alles-zum-thema-sucht/), (https://www.quarks.de/gesellschaft/psychologie/stress-wie-er-uns-pusht-und-bremst/)